Journal of Saudi Chemical Society (2016) xxx, xxx–xxx

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

$POCl_3$ catalyzed, one-step, solvent-free synthesis of some novel thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives as antimicrobial agent

Dipen K. Sureja [a,*], **Kantilal R. Vadalia** [b]

[a] *Department of Pharmacy, Sumandeep Vidyapeeth, Po – Piparia, Ta – Waghodia, Vadodara 391760, Gujarat, India*
[b] *Atmiya Institute of Pharmacy, Yogidham Gurukul, Kalawad road, Rajkot 360005, Gujarat, India*

Received 23 May 2016; revised 6 July 2016; accepted 13 July 2016

KEYWORDS

$POCl_3$;
Thieno[2,3-*d*]pyrimidin-4(3*H*)-one;
Conventional heating;
MW assisted synthesis;
Antimicrobial activity

Abstract A $POCl_3$ catalyzed, efficient, one-step and solvent-free synthesis of novel thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives from 2-amino-4,5-substitutedthiophene-3-carbonitrile has been developed under conventional heating and microwave irradiation. The formation of compounds was confirmed using elemental analysis and spectroscopic techniques like IR, NMR (^1H and ^{13}C) and mass spectroscopy. Furthermore, they were screened *in vitro* to study their antimicrobial activity, which shows weak to moderate activity against all tested microorganisms.

1. Introduction

In the current era, antibiotics and synthetic antimicrobial agents have changed the scenario of the medical field in the treatment of various bacterial and fungal infections. However, occurrence of various drug-resistant microbial strains posed a concrete contest to the medicinal chemists [1]. So, the medicinal chemists are working to develop new chemical entities to conquer drug resistant strains.

Thienopyrimidine, having structural resemblance to purine, is an important class of therapeutic drugs having a broad range of biological activities. Various diversified biological activities such as antibacterial [2–5], antimicrobial [6–8], antiviral [9], anti-HIV and anti-HSV [3], anti-avian influenza virus (H5N1) [10], anti-inflammatory [5,7], analgesic [5,11], antidepressant and sedative [11] have been reported for thienopyrimidine derivatives.

Various synthetic approaches have been utilized for the synthesis of thienopyrimidines [12]. Recently, Bakavoli et al. [4] used molecular iodine as an oxidizing agent for the synthesis of thienopyrimidine via an oxidative heterocyclisation reaction. However, the synthesis of thienopyrimidine from 2-amino-4,5-substitutedthiophene-3-carbonitrile requires two steps, we tried to develop a single step and solvent-free method to generate a series of thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives.

In recent times, microwave assisted synthesis of medicinal compounds has gained appreciation among the synthetic chemists due to their improved selectivity, shorter reaction time, eco-friendliness and superior work-up procedures [13]. Litera-

* Corresponding author.
E-mail address: dipensureja@gmail.com (D.K. Sureja).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2016.07.004

ture survey also revealed the importance of the microwave irradiation technique for the synthesis of thienopyrimidine from 2-amino-4,5-substituted-3-carbethoxythiophene [14,15].

So, herewith we are reporting the efficient synthesis of thieno[2,3-*d*] pyrimidin-4(3*H*)-one derivatives from 2-amino-4,5-substitutedthiophene-3-carbonitrile by conventional heating as well as by microwave assisted synthesis using $POCl_3$ as a chlorinating and oxidizing agent.

2. Experimental protocols

2.1. Materials and methods

All the chemicals and solvents used were of LR grade, obtained from SD fine chemicals and Merck (Mumbai, India). The progress of reaction was tested on precoated silica gel F_{254} plates obtained from Merck (Mumbai, India) using the mobile phase toluene and ethyl acetate in 7:3 ratio. Iodine chamber and UV lamp (λ = 254 nm) were used for visualization of the spots. Chemline CL726 melting point apparatus was used for measurement of melting points in an open capillary tube and are uncorrected. The IR spectra (ν_{max}, cm^{-1}) were recorded on Shimadzu FT-IR 157 spectrophotometer as KBr disk. ^1H NMR and ^{13}C NMR (δ, ppm) spectra were recorded on Bruker advance III 500 MHz NMR spectrophotometer operating at 500 MHz and 125 MHz for ^1H and ^{13}C respectively in $CDCl_3$/DMSO-d_6 using TMS as reference standard. Mass spectra were recorded on Shimadzu GC-MS-QP2010 mass spectrometer. Elementar Vario EL III CHN analyzer was used for elemental analysis and results were found within ±0.4% of the calculated value.

2.2. General procedure for preparation of 2-amino-4,5-substitutedthiophene-3-carbonitrile (*1f–g*)

4-Methylcyclohexanone or 1,3-cyclohexanedione (0.01 M), malanonitrile (0.01 M), sulfur (0.01 M) and ethanol (10 mL) were mixed in a conical flask. The reaction mixture was warmed up to 40-50 °C on a water bath and then diethylamine (1 mL) was added with constant stirring in such a way that the temperature does not exceed 50 °C. Stirring was continued for 1-2 h till solid crystals gets separated. The reaction mixture was then cooled and kept in a refrigerator. The fine crystals thus obtained were filtered, dried and recrystallized from a suitable solvent to give target compounds in good yields.

2.2.1. 2-Amino-5-ethyl-4-methylthiophene-3-carbonitrile (*1a*)

Yield 68% (Ethanol); m.p. 102-3 °C; IR (KBr, cm^{-1}): 3332, 3185, 2968, 2912, 2215, 1622; ^1H NMR ($CDCl_3$, δ): 1.39 (t, 3H, -CH_3), 2.37 (s, 3H, -CH_3), 2.99 (q, 2H, -CH_2), 8.27 (s, 2H, -NH_2, D_2O exchangeable); ^{13}C NMR ($CDCl_3$, δ): 9.68, 13.85, 20.73, 84.22, 116.4, 128.1, 135.07, 149.1; MS: *m/z* 124 (100%), 166 (M^+); Anal. Calcd. (Found) for $C_8H_{10}N_2S$: C, 57.80 (57.83); H, 6.06 (6.10); N, 16.85 (16.81).

2.2.2. 2-Amino-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (*1f*)

Yield 84% (Ethanol); m. p. 144-6 °C; IR (KBr, cm^{-1}): 3334, 3190, 2969, 2900, 2219, 1621; ^1H NMR ($CDCl_3$, δ): 1.24 (d, 3H, –CH_3), 2.05 (m, 1H, ═CH), 2.22 (d, 2H, -CH_2), 2.46 (t, 2H, -CH_2), 2.74 (t, 2H, -CH_2), 8.29 (s, 2H, -NH_2, D_2O exchangeable); ^{13}C NMR ($CDCl_3$, δ): 20.33, 21.73, 28.3, 30.1, 31.55, 84.2, 116.4, 135.0, 138.1, 149.2; MS: *m/z* 150 (100%), 192 (M^+); Anal. Calcd. (Found) for $C_{10}H_{12}N_2S$: C, 62.46 (62.33); H, 6.29 (6.28); N, 14.57 (14.61).

2.2.3. 2-Amino-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (*1g*)

Yield 74% (Dioxane); m.p. 215-7 °C; IR (KBr, cm^{-1}): 3345, 3198, 2968, 2909, 2214, 1665, 1622; ^1H NMR (DMSO-d_6, δ): 2.25 (m, 2H, -CH_2), 2.85 (t, 2H, -CH_2), 3.01 (t, 2H, -CH_2), 8.30 (s, 2H, -NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ): 22.5, 22.7, 37.5, 84.25, 116.6, 139.5, 149.2, 163.7; MS: *m/z* 150 (100%), 192 (M^+); Anal. Calcd. (Found) for $C_9H_8N_2OS$: C, 56.23 (56.33); H, 4.19 (4.10); N, 14.57 (14.63).

2.3. General procedure for preparation of thieno[2,3-d] pyrimidin-4(3H)-one derivatives (*2a–o*)

2.3.1. Conventional synthesis

2-Amino-4,5-substitutedthiophene-3-carbonitrile (**1a–g**) (1 mM) was dissolved in appropriate aliphatic acid (2 mL). Then $POCl_3$ (0.2 mL) was added drop wise and the reaction mixture has been kept for reflux on a boiling water bath. The reaction progress was supervised using TLC. After completion of the reaction, the mixture was poured on ice-cold water (50 mL) and crude precipitates thus formed were filtered, washed with 10% sodium bicarbonate solution, dried and recrystallized from a suitable solvent.

2.3.2. Microwave assisted synthesis

A mixture of 2-amino-4,5-substitutedthiophene-3-carbonitrile (**1a–g**) (1 mM), appropriate aliphatic acid (2 mL) and alumina (0.5 g) were finely crushed and transferred to a glass vial and then phosphorus oxychloride (0.2 mL) was added to this mixture. The glass vial was then capped and microwaves were irradiated in a microwave oven (CEM, Discover microwave lab station, 2450 MHz with temperature control) at the power of 960 W for 2-4 min. After the completion of reaction (reaction monitoring by TLC), the mixture was poured on ice-cold water (50 mL). The precipitated product was filtered and washed with 10% sodium bicarbonate solution to give the desired compounds.

2.3.3. 6-Ethyl-5-methylthieno[2,3-d]pyrimidin-4(3H)-one (*2a*)

IR (KBr, cm^{-1}): 3164, 3071, 2969, 2910, 1667, 1578; ^1H NMR (DMSO-d_6, δ): 1.32 (t, 3H, –CH_3), 2.38 (s, 3H, –CH_3), 2.90 (q, 2H, –CH_2), 8.10 (s, 1H, ═CH), 11.90 (s, 1H, –NH of pyrimidine, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ): 9.68, 13.85, 20.53, 118.4, 132.1, 134.07, 145.7, 156.2, 161.0; MS: *m/z* 194 (100%, M^+).

2.3.4. 6-Ethyl-2,5-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (*2b*)

IR (KBr, cm^{-1}): 3156, 3067, 2976, 2918, 1665, 1574; ^1H NMR ($CDCl_3$, δ): 1.32 (t, 3H, –CH_3), 2.37 (s, 3H, –CH_3), 2.49 (s, 3H, –CH_3), 2.91 (q, 2H, –CH_2), 11.87 (s, 1H, –NH of pyrimidine, D_2O exchangeable); ^{13}C NMR ($CDCl_3$, δ): 9.7, 13.9, 20.5, 21.4, 118.3, 131.9, 133.87, 153.7, 156.2, 161.0; MS: *m/z* 208 (100%, M^+).

Please cite this article in press as: D.K. Sureja, K.R. Vadalia, $POCl_3$ catalyzed, one-step, solvent-free synthesis of some novel thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives as antimicrobial agentd]pyrimidin-4(3*H*)-one derivatives –>, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.07.004